REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 60-104 are currently pending. Claims 60, 65, 70, 80, 85, 90, 95 and 100 are amended, and new claims 105-109 are added, by way of the present Amendment. Basis for these amendments and new claims may be found throughout the specification and claims as-filed, especially at least pages 1-6, 11-15, 17-20, 22-23, the synthetic Examples and the formulation Examples , as well as in the specification and claims originally filed in predecessor Application No. 08/930,796, now U.S. Patent No. 5,981,776, which claims the compounds *per se*.

Claims 75-79 are canceled by way of the present Amendment. Applications reserve the right to file a continuation or divisional application directed to any subject matter canceled by way of this Amendment.

Before turning to the specific rejections of the claims set forth in the outstanding Office Action, Applicants make the following comments. First, Applicants again thank the Examiner for calling Applicants' representative to suggest amendments to the claims on March 18, 2002. Applicants note that although Applicants amended the claims as the Examiner requested, the claims were not found allowable.

Applicants further note that the last three Office Actions issued for the captioned application (mail dated March 28, 2001, September 18, 2001 and December 19, 2002) have been non-final. Thus, although Applicants have discussed this application with the Examiner, as well as with the Examiner's supervisor, prosecution does not appear to be advancing.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 75-79 stand rejected under 35 U.S.C. 112, first paragraph, as purportedly reciting subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims stand rejected for the recitation of a method for "inhibiting differentiation of keratinocytes" in claim 75. This language does not appear in any of the claims now pending in the application, in light of the present Amendment. Thus, Applicants submit this rejection is mooted.

Claims 60-104 stand rejected under 35 U.S.C. 112, first paragraph, as purportedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse.

As stated in *Ex parte Forman* (230 USPQ 546 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As, the Office is aware, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. § 112, first paragraph. Thus, not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (Bd. Pat. App. & Int. 1992). Applicants submit that the specification provides adequate description of how to use the methods described; moreover, provided a Declaration pursuant to 37 C.F.R. § 1.132, explaining how the information in the specification provided the skilled artisan with adequate detail.

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification

disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth. *See* MPEP § 2164.04.

Applicants respectfully submit that the claims, as amended herein, are enabled by the specification. This argument is supported by the Declaration of Dr. Demarchez, filed by Applicants on September 18, 2000, and that the Examiner has failed to provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure.

Quantity of experimentation necessary, guidance provided and working examples

Applicants submit that the undue experimentation is not necessary in order for the skilled artisan to practice the methods of the claimed invention. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

To that end, Applicants submit that the specification provides methods of making the compounds now patented in the parent case, methods of using the

compounds of the claimed invention, as well as exact formulations for use in using the claimed methods to treat specific conditions (*see* Examples). In addition, Applicants submitted a Declaration by Dr. Demarchez, which supports the argument that undue experimentation is not required, as the art is very familiar with this type of experimentation.

In his Declaration, Dr. Demarchez provided and discussed data obtained in experiments conducted by the Applicants as well as statements based on his knowledge of the state of the art. In particular, the Declaration supports the conclusion that several compounds according to the invention have been demonstrated to have biological activity and therapeutic utility. The Declaration also provides a discussion of published references that document the well known scientific finding that retinoids have established utility as therapeutic agents. Copies of the documents referred to in the Declaration in this regard were provided to the Examiner on July 18, 2000 and in addition, the Declaration provides the results of *in vivo* assay tests showing how a compound according to the invention has biological activity in ear edema.

As discussed in the Declaration, the fact that the compounds according to the invention have therapeutic utility was further substantiated by data which has been obtained by the present inventors relating to several compounds of the invention. Specifically, using the F9 test (which is an accepted assay for identifying RAR-type agonists), the present inventors demonstrated that the compounds of Example 2

and Example 6 are RAR-type agonists (*see* the data presented in Table 1 in the Declaration).

Moreover, in another accepted assay (as described in Levin *et al.*, *Nature*, Vol. 355, pp. 359-361 (1992), and in Allenby *et al.*, *Proc. Natl. Acad. Sci. USA*, Vol. 90, pp. 30-34 (1993)) the inventors confirmed that the compounds of Example 2 and Example 4 function as RXR agonists (see the data presented in Table 2 in the Declaration). As discussed above, it is known in the art that such agonists find accepted usage as pharmacological agents, in particular for treatment of disorders involving cell proliferation and differentiation and in particular keratinization related disorders.

In particular, the Examiner is again respectfully referred to Safonova *et al.*, (*Biochemical and Biophysical Research Communications*, Vol. 204, No. 2, 1994) which discloses the usage of such agonists on cell differentiation and potential therapeutic utility. Moreover, Hong *et al.* (*Retinoids and Human Cancer*, from *The Retinoids: Biology, Chemistry, and Medicine*, 2nd Ed., 1994) reviews the accepted usage of retinoids in the treatment of human cancer. The reference identifies numerous retinoids having such utility including all-trans retinoic acid, isotretoin, etretinate, fenretinide, and arotinoids. Also, as summarized in Dr. Demarchez's Declaration, Lippman and DiGiovanna (*Retinoids and Skin Cancer*) teaches the potential usage of retinoids in treating such disorder and the use of single agent retinoid therapies in advanced malignant disease such as acute promyelocytic leukemia, mycosis fungoides, and skin cancer. The authors indicate that retinoids

show great therapeutic promise in such treatments. Also, as discussed in the Declaration, Kavanagh *et al.* (*Retinoids and Cervical Cancer*) disclose that topical trans-retinoic acid is active in the treatment of cervical carcinogenesis with complete lesion reversal obtained in one trial.

In particular, the Examiner is referred to Table 2, which summarizes the results of studies of local retinoid activity and toxicity in the treatment of cervical displasia. Still further, Meyskens *et al.* (*Role of topical tretinoin in melanoma and dysplastic nevi*, Vol. 15, No. 4 (1986)) discloses the usage of topical tretinoin in the treatment of melanoma and dysplastic nevi, with the authors concluding that such administration had activity against melanoma, and its precursor conditions.

Therefore, based on the foregoing, Applicants respectfully submit that the efficacy of retinoid compounds as pharmaceutical agents is accepted in the art. Therefore, based on the data provided in the Declaration demonstrating that compounds according to the invention function as RAR and RXR agonists, it is reasonable to conclude that they will exhibit desirable pharmacological properties and useful in the treatment of the recited conditions.

Also, the retinoic acid activity of the of compounds according to the invention has further been demonstrated in an *in vivo* assay which measures the effect of compounds according to the invention on ear edema induced by topical administration of a compound according to the invention, specifically the compound of Example 2 (see the data of Table 3 in the Declaration). These results, which are summarized in Dr. Demarchez's Declaration, further support that the retinoic acid of

Example 2 when applied topically induces an augmentation of the ear oedma. This data provides further evidence that compounds according to the invention, and specifically the elected compound, may be used in treatment of the recited conditions, in particular treatment of dermatological conditions such as those associated with differentiation and proliferation.

State of the prior art, relative skill of those in that art predictability and unpredictability of the art

With regard to the state of the art, as well as to the level of skill in the art and the predictability of the art, Applicants submit that the skill level in this art is high. Applicants have provided multiple references, in the Declaration of Dr. Demarchez, showing that research and treatment methods are well known. Thus, the skilled artisan would not have difficulty fine tuning the claimed methods if needed. With regard to predictability, Applicants again turn the Examiner's attention to the data and experimentation provided by the Applicant.

Thus, Applicants submit that in light of the formulations and methods of using the claimed compounds as provided in the instant specification, as well as in the data and references provided in the Declaration of Dr. Demarchez, the skilled artisan would not only be able to successfully practice the claimed methods, but would also have an expectation of therapeutic success in treating the claimed conditions.

The outstanding Office Action comments on the references cited in the Declaration of Dr. Demarchez in light of claims 42-55. Applicants respectfully note that as of the mail date of the present Office Action, December 19, 2002, claims 42-55 were no longer pending, as acknowledged on the Office Action Summary page (claims 60-104 are pending).

However, Applicants provide the following comments regarding the Examiner's arguments, in the context of the present claims.

The Office Action states that even if it is true that the claimed compounds are in fact "retinoids", all retinoids do not exhibit the same activities, either *in vitro* or *in vivo*, and moreover, many retinoids are in fact ineffective in treatment of various proliferative disorders. The Office Action makes the same comment with regard to the compounds discussed in the references discussed in the Declaration of Dr. Demarchez. The Office Action argues that Applicants have applied the label "retinoid" to the claimed compounds, but that there is no agreed upon standard as to what the structural, biochemical or physical properties might be that are either necessary or sufficient for a compound to be classified in this way. Specifically, the Examiner states that "Some chemists might apply the term "retinoid" because the UV/VIS spectrophotometric properties of a given compound are similar to retinal.... A botanist may have another view entirely of what a "retinoid" is."

Applicants respectfully note that the claims of the invention are construed at the level of the skilled artisan. In the case of the present invention, the skilled artisan is not necessarily a physical chemist, and certainly not a botanist. The

possibility that a botanist, who is not skilled in the art of the present invention, may become confused by the use of the term "retinoid" is irrelevant to the patentability of the present invention. Rather, what is relevant is the ease at which the skilled artisan would be able to make and use the claimed invention. Applicants submit that the skilled artisan would find the present claims to be enabled.

Applicants further note that it appears that the Examiner has not given weight to the Declaration submitted by Demarchez. Applicant may submit factual affidavits under 37 C.F.R. § 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. MPEP § 2164.05. It is the responsibility of the primary examiner to personally review and decide whether affidavits or declarations submitted under 37 C.F.R. § 1.132 for the purpose of traversing grounds of rejection are responsive to the rejection and present sufficient facts to overcome the rejection. MPEP § 716. Thus, Applicants submit that proper weight should be given to the Declaration of Dr. Demarchez.

The Examiner cites to the following references in support of his arguments:

- Benedetti (*Blood* **87** (5) 1939-50, 1996);
- Byers S (*Endocrinology* **137** (8) 3265-73, 1996);
- Chandraratna R A (*Journal of the American Academy of Dermatology* 37 (2 Pt 3), S12-S12, 1997);

- Chen S *et al.* (*Journal of Pharmacy and Pharmacology* **47** (8) 626-31, 1995);
- Dockx P. (*British Journal of Dermatology* **133** (3) 426-32, 1995);
- Elder J T *et al.* (*Journal of Investigative Dermatology* **106** (3) 517-21, 1996);
- Kinoshita *et al.* (*Blood*, **95** (9) 282 1-8, 2000);
- Miller W. H. *et al.* (*Blood* **85** (11) 3021-7, 1995);
- Muccio D. *et al.* (*J. Med Chem.* **41** (10)1679-87, 1998);
- Paraskevaidis A *et al.* (*Dermatology* **196** (1) 171-5. 1998);
- Sakaue *et al.* (*Molecular Pharmacology* **55** (4) 668-76, 1999);
- Shiohara M *et al.* (*Blood* **93** (6) 2057-66, 1999) discloses that SRi 1363 (Retinoid B);
- Sun S Y *et al.* (*Cancer Research* **57** (21) 493 1-9, 1997);
- Tashima T *et al.* (*Chemical and Pharmaceutical Bulletin* **45** (11) 1805-13, 1997);
- Tockman, (*IARC Scientific Publications* **154** 257-70, 2001);
- Wan H *et al.* (*Cancer Research* **61** (2) 556-64, 2001; and
- Weinstein G. D. *et al.* (*Journal of the American Academy of Dermatology* **37** (1) 85-92,1997).

The Examiner argues that if "applicants believe that *in vitro* data (obtained on retinoids) is indeed predictive of therapeutic efficacy, then it is suggested that

applicants read through each of the references cited by the examiner, and explain how it is that they could have predicted the failure of each retinoid to be therapeutically effective", in order to advance prosecution. Applicants respectively submit that this suggestion is improper. There is no burden on Applicants to go through references cited by the Examiner and explain the issues in each reference to the Examiner. The burden is on the Examiner to show how the references he cites support the rejections of the claims. Once this burden is met, Applicants must address rejections to their claims, and address the issues concerning the present claims. However, Applicants do not bear a burden to show "enablement" or "predictability" of references cited by the Examiner himself.

Finally, Applicants note that although the rejection of claims 60-104 presented in the outstanding Office Action is presented as a rejection under 35 U.S.C. § 112, first paragraph (enablement), the rejection appears to actually be a rejection pursuant to 35 U.S.C. § 101 (utility). For example, the outstanding Office Action comments on the purported lack of credible use for the methods of the claimed invention. Applicants note that a rejection under 35 U.S.C. § 101 would clearly be inappropriate in the present case, as no incredible utility has been set forth for the claimed invention.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 60-104 stand rejected under 35 U.S.C. §112 second paragraph, as purportedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the independent claims are rejected for the recitation of "inflicted". Independent claims 60, 65, 70, 80, 85, 90, 95 and 100 have been amended herein, and no longer recite "inflicted". Independent claim 75 has been canceled. Thus, Applicants submit this rejection is mooted.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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